INTRODUCTION

Weinberg and Hanahan\textsuperscript{1} in 2011 revised the hallmark of cancer and defined ten vital properties that enhance cancer evolution and growth. The hallmark of cancer as revised by them include: sustainment of proliferative signaling; evasion of growth suppressors; avoidance of immune destruction; enablement of replicative immortality; tumor-promoting inflammation; activation of invasion and metastasis; induction of angiogenesis; genome instability and mutation; resistance to cell death; and deregulation of cellular energetics\textsuperscript{2,3}. Several researchers have proven the crucial role HMGB1 players in a variety of cancers including colon, breast, lung, prostate, cervical, skin, kidney, stomach, pancreatic, liver, bone, glioma and blood cancers\textsuperscript{4-6}. Kang et al\textsuperscript{7} stated that depending on the context and the disease conditions as well as location and modification, HMGB1 acts as both a tumor suppressor and an oncogenic factor in carcinogenesis and cancer remedy. HMGB1 is a hoarded non-histone chromatin protein partaking in a variety cellular functions, with an imperative role in nucleosomal stability, transcriptional control, and proinflammatory reactions\textsuperscript{7-10}. Ferrari et al\textsuperscript{11} indicated that the HMGB1 gene compressing of six exons and encodes a 215-amino acid polypeptide is located on the human chromosome 13q12. Muller and colleagues indicated that HMGB1 function as a cotranscriptional factor in the intracellular space. They further explained that it binds to the minor groove of linear DNA, stabilizing nucleosomes...
and mobilizing and collaborating with so many transcription factors such as p53, NF-κB, variable diversity joining (VDJ) recombination activating proteins 1 (RAG1), homeobox-containing proteins, and steroid hormone receptors.11,12

HMGB1 can be ‘passively released’ into the extracellular space from damaged or necrotic cells, which operate as a damage-associated molecular pattern (DAMP) molecule known as ‘alarmins,’ chemotactic necrotic markers that activate innate responses and initiate tissue repair.13 Research has proven that HMGB1 binds to a variety of receptors, Toll-like receptors (TLRs) and receptor for advanced glycation end products (RAGE)14 and receptor for advanced glycation end products (RAGE).15 Apetoh et al15,16 have indicated that HMGB1 can be Hypo-acetylated when it is passively secreted from necrotic or dying cancer cells and trigger antigen-presenting cells (APC) via TLR-4 leading to induction of antineoplastic immune response. Kazama et al17 further stated that inflammatory cells such as monocytes, macrophages, and dendritic cells (DCs), during apoptosis actively release hyperacetylated form of HMGB1, which induces immunological tolerance. Our review focuses on the clinicopathological and therapeutic role of HMGB1 in cancer.

HMGB1 and cancer immunity

The tumor microenvironment is made up of tumor cells and noncancer cells, comprising numerous immune cells. Extracellular HMGB1 intervenes the interrelatiion between cells in the tumor microenvironment by numerous receptors (e.g., RAGE and TLR-4). These receptors facilitate cancer growth and metastasis by numerous mechanisms that include sustenance of the inflammatory microenvironment, fulfillment of metabolic requirements, facilitation of invasion and metastasis.18-20 van Beijnum et al21 proposed multiple sources of HMGB1 secretion during tumor formation and progressing. They indicated that while necrotic cancer cells may leak HMGB1 into the extracellular space, cancer-associated macrophages can actively secrete HMGB1 and vascular endothelial growth factor (VEGF). They argue that anti-HMGB1 antibodies were able to antagonize new blood vessel formation in their research models. This means that functional blocking of endothelial HMGB1 service as a restraint in the process of angiogenesis. They concluded that HMGB1 exercise pleiotropic effects, stimulating cancer growth, metastasis and angiogenesis. He et al22 demonstrated that cancer-triggered HMGB1 as a constitutive danger signal, activates a T-cell-dependent positive loop by acting on the innate immune cells first to prime cancer-specific T cells, which in turn release cytokine lymphotoxin (LTs), migrate to the cancer, upregulate chemokines, and recruit macrophages to promote cancer progression, which is associated with more HMGB1. They proposed that this cancer-specific T-cell-dependent loop could be an essential contributor to pre-cancer to malignant cancer.22

HMGB1 and cancer growth signals

HMGB1 triggers signaling pathways comprising protein kinase B (AKT), mitogen-activated protein kinases (MAPKs), and NF-κB, which play central role in cancer growth (Figure 1). HMGB1 facilitates phosphatidylinositol 3-kinase/Akt pathway stimulation in neutrophils23,24. It’s well known that AKT frequently dysregulated in human cancers although it is a key watchdog in cell proliferation and survival. Fan et al25 demonstrated that TLR-4-dependent stimulation of NAD(P)H oxidase in vitro was initiated when neutrophils were induced with recombinant HMGB1 as well as acceleration reactive oxygen species (ROS) generation through MyD88-IRAK4-p38 MAPK and MyD88-IRAK4-AKT signaling pathways. Degryse et al26 indicated that HMGB1 interaction with RAGE champions the stimulation of NF-κB and ERK1/2, p38 and SAPK/JNK kinases. MyD88-dependent triggering of NF-κB is initiated by HMGB1 when it binds to TLR-2 and TLR-4.23,25,27. It’s, therefore, evident that MAPKs and NF-κB pathways are vital signal pathways connecting HMGB1’s proinflammatory function. For Kalinina et al28 obviation of MEK1/MEK2, protein kinase C, and PI-3/AKT hinder cytokine-mediated HMGB1 expression.

Apoptosis and Carcinogenesis

Many researchers have disclosed that intracellular HMGB1 could be a tumor suppressor. Jiao et al29 demonstrated that nuclear HMGB1 binds to tumor suppressor RB, which champions RB-dependent G1 blockade and apoptosis activation and prevents carcinoigenicity in breast cancer cells in vitro and in vivo. Several studies have also indicated that nuclear HMGB1 is a significant architectural factor with DNA chaperone function. It is now clear that loss of HMGB1 champion’s genome instability with telomere shortening, which is a powerful force in carcinogenesis. HMGB1 shields mammalian cells against numerous death stimuli, including ultraviolet radiation, CD95-, TRAIL-, Casp-8-, and Bax-triggered apoptosis.30 HMGB1 elevation through gene transfection ren-
HMGB1 is a critical regulator of autophagy in cancer cells. Several studies have demonstrated that HMGB1 is choosily secreted from cancer cells undergoing autophagy (8,16). Studies have further proven that deficiencies of autophagy gene (e.g., Beclin-1, ATG5, UVRAG, Bif-1) accelerate carcinogenesis due to genome instability, inflammation, and organelle injury. Studies have also shown that cytoplasmic HMGB1 can directly bind to autophagy protein Beclin-1, disrupting Beclin-1/Bcl-2 interaction and sustaining autophagy. Furthermore, endogenous knockdown of HMGB1 with siRNA or inhibition of its release with small-molecule inhibitors, eliminated the defensive influence of autophagy and augmented cancer cell sensitivity to numerous clinically advantageous drugs. Moreover, autophagy may be imperative in the regulation of cancer advancement and progression as well as influential potentials of cancer cells to anticancer therapy. Therefore, autophagy deficiencies promote carcinogenesis and augmented therapy sensitivity. 

**Autophagy and Carcinogenesis**

Autophagy is a lysosome-mediated, self-degradation process that safeguards normal cells, but also stimulates cancer cell survival under stress. It is a process in which subcellular membranes undergo dynamic morphological variations causing intracellular degradation of proteins, cytoplasmic organelles and pathogens; it is a mechanism subjugated by cancer cells for survival and used in determining cancer response to anticancer therapy. Accumulated evidence suggests that endogenous HMGB1 is a critical regulator of autophagy in cancer cells. Several studies have demonstrated that HMGB1 is choosily secreted from cancer cells undergoing autophagy (8,16). Studies have further proven that deficiencies of autophagy gene (e.g., Beclin-1, ATG5, UVRAG, Bif-1) accelerate carcinogenesis due to genome instability, inflammation, and organelle injury. Studies have also shown that cytoplasmic HMGB1 can directly bind to autophagy protein Beclin-1, disrupting Beclin-1/Bcl-2 interaction and sustaining autophagy. Furthermore, endogenous knockdown of HMGB1 with siRNA or inhibition of its release with small-molecule inhibitors, eliminated the defensive influence of autophagy and augmented cancer cell sensitivity to numerous clinically advantageous drugs. Moreover, autophagy may be imperative in the regulation of cancer advancement and progression as well as influential potentials of cancer cells to anticancer therapy. Therefore, autophagy deficiencies promote carcinogenesis and augmented therapy sensitivity.

**Fig. 1.** HMGB1 triggers signaling pathways comprising protein kinase B (AKT), mitogen-activated protein kinases (MAPKs), and NF-κB, which play central role in cancer growth. HMGB1 binds to numerous seemingly disparate proteins, comprising pRb, by identifying short amino acid sequence. The HMGB1-RB interaction leads to HMGB1-mediated E2F and cyclin A transcriptional suppression resulting in cell growth reticence, G1 cell cycle blockade, apoptosis stimulation, and cancer growth suppression.
**HMGB1 and Cancer Anti-Growth Signals**

Jiao et al. again demonstrated that HMGB1 suppressed growth of MCF-7 cancer xenografts in nude mice, whereas LXCCX-defective HMGB1 absolutely dispossess antitumor growth activity. Krynetskaia et al. indicated that HMGB1-deficient MEFs reduces caspase activity and harmonize cell cycle blockade resulting in genotoxic stress triggered by antimetabolite drugs. Dintilhac and Bernues indicated that pRB restricts proliferation during hypophosphorylation by sequestering and modifying the role of the E2F family of transcription factors. HMGB1 binds to numerous seemingly disparate proteins, comprising pRB, by identifying short amino acid sequences. An HMGB1-RB interaction (Figure 1) is essential for the HMGB1-mediated E2F and cyclin A transcriptional suppression which leads to cell growth reticence, GI cell cycle blockade, apoptosis stimulation, and cancer growth suppression, but is not required for radiosensitization. Voit et al. proposed that HMG box comprising transcription factor UBF is the key target for pRB-induced transcriptional suppression.

**HMGB1 in cancer microinflammatory environment**

Cancer inflammatory retorts, also known as “microinflammatory environment”, is a novel mechanism by which cancer facilitates immune response to malignant cancerous cells. These inflammatory occurrences during cancer have multifarious purposes in cancer development, advancement and immune response. Studies have proven that HMGB1 has a duplicitous characteristic response to the immune system in a broad-spectrum. Furthermore, an inflammatory microenvironment facilitates cancer development and has efficient immune identification, which leads to efficient eradication of cancerous cells. Chronic inflammation is fundamental for cancer growth. This phenomenon is a hypothesis that is supported by countless remarks such as: 1) cancer frequently originates from locations with chronic inflammation, immune cells are seen in virtually all kinds of malignancies; 2) tentative inhibition of inflammatory intermediaries such as HMGB1 blocks malignancy advancement as well as delivery of anti-inflammatory drugs, which has proven to decrease the menace of cancer in some cases. Studies have shown that HMGB1 exercises manifold proinflammatory roles such as stimulation and triggering of proinflammatory cytokines through NF-κB, IL-1β as well as facilitation of angiogenesis and metastasis at the cancer microenvironment. Furthermore, the inflammatory environment can support itself during positive feedback loops immediately the secretion of free radicals and proinflammatory cytokines exceed a certain quantity. Moreover, the permanent existence of free radicals and mutagenic factors triggers cell mortification and dedifferentiation, which result in the inductee of a cancerous event. Nevertheless, cancer development is subsequently facilitated by inflammatory intermediaries till the cancerous tissue it is able to withstand inflammation by cytokine secretion as well as different feedback loops.

**HMGB1 and lymphangiogenesis in cancer environment**

Lymphangiogenesis is associated with a multifaceted multistep process pertaining to endothelial cell proliferation, migration, and tube formation. Prognosis in malignancies is affected significantly by metastatic dissemination of the primary cancer. The two most crucial channels by which cancer cells spread and invade are the lymphatic and blood stream. Stacker et al. indicated that lymph node is the most frequent pathway for malignant solid cancer metastasis, especially cancer which is the initial process of cancer cells metastasis closely associated with the poor survival. The cancer microenvironment is usually a complex process consisting of cancer cells and noncancer cells as well as endothelial cells (ECs), cancer-associated fibroblasts (CAFs), cancer-associated macrophages (TAMs), and noncellular components or pro-cancer mediators. Qiu et al. demonstrated that HMGB1 can function as a lymphangiogenic growth factor by activating LEC proliferation, migration, and tube formation in a dose and time dependent manner. Salven et al. discovered a constructive interrelation between the secretion of VEGF-C in human malignant tissue with unfavorable clinicopathological qualities such as lymphatic invasion and lymph node metastasis. They indicated that the secretion of VEGF-C mRNA was amplified in numerous of human cancers. These cancers comprise of breast, gastric, colorectal, esophageal, prostate, pancreas, cervical, thyroid, non-small-cell lung cancers, lung adenocarcinoma and laryngeal cancers. Clinically imperative areas of concentration are the interrelation between VEGF-C and -D secretion, intra- and pericancer lymphatic density, lymphatic and venous invasion, lymph node metastasis and survival.
Zhang et al\textsuperscript{47} proposed that the unstimulated quiescent TAMs from ascites of epithelial ovarian cancer synthetized and secreted a series of cytokines, and when HMGB1 was present, the lymph angiogenesis process was extensively potentiated. They, therefore, concluded that the co-treatment of exogenous rHMGB1 and TAMs may strengthen prolymphangiogenic property. Biswas et al\textsuperscript{51} are also of the view that TAMs, which symbolize a specific macrophage population with significant properties of M2 cells, could express different functional programs in reaction to the microenvironment signals\textsuperscript{47}. The prolymphangiogenic effect of HMGB1 linking with TAMs could be that HMGB1 interacts with its receptors on TAM and facilitates several intracellular signal transduction pathways such as Ras/MAPK, NF-κB, Rac, STAT3, and Cdc42, resulting in an accelerated secretion of the lymphangiogenic growth factors\textsuperscript{47,51}. The interaction between HMGB1 and TAMs could, therefore, prime the amplified prolymphangiogenic property (Figure 2). The clinical value of HMGB1 linking with TAMs might serve as a potentially key marker with respect to lymphatic metastasis\textsuperscript{47}.

\textbf{HMGB1 and cancer Angiogenesis}

Angiogenesis signifies the commencement of contemporary blood vessels out of predecessor’s vessels. It is the primary sequence connected to imitation, progression, and wound healing\textsuperscript{52,53}. The growth of contemporary vessels is very essential in the commencement and advancement of numerous diseases as well as cancer\textsuperscript{52,54}. It is ex-

![](image)

\textbf{Fig. 2.} Cancer cells secrete both HMGB1 and TAM. HMGB1 interacts with its receptors on TAM facilitates several intracellular signal transduction pathways such as Ras/MAPK, NF-κB, Rac, STAT3, and Cdc42, resulting in an accelerated secretion of the lymphangiogenic growth factors. These interactions therefore result in lymphatic metastasis.
tensively established that cancer development is angiogenesis-dependent and inhibiting this route is considered as an auspicious curative modality to damage cancer development\textsuperscript{52,55}. The conception of this revolutionary assumption leads to the exploitation and development of many anti-angiogenic agents in various cancers. Nevertheless, single antiangiogenic drugs are not as efficient as originally anticipated\textsuperscript{52}. Correspondingly, amendments have been accomplished by coalescing antiangiogenic therapeutic agents and typical chemotherapy with remunerations in advancement-free and improved generally survival rate\textsuperscript{52,56,57}. However, unfavorable hitches of these dual therapeutic modalities comprise of resistance, decreased distribution of these agents inside the cancerous cells, and amplified cancer hypoxia, which in turn may optimistically aggravate cancer growth and metastasis\textsuperscript{52,56}. Nonetheless, a substantial number of cases frequently does not have any added advantage with the use of these antiangiogenic remedies\textsuperscript{52,57}. The development of contemporary blood vessels is strictly controlled and associated with the synchronized interrelations between a congregation of diverse cell categories, cytokines, growth factors, and extracellular matrix (ECM) components\textsuperscript{52,54,58,59}. Modifications of ECM permit endothelial cell (EC) development and is preferential triggered by numerous proteases\textsuperscript{52}.

Matrix metalloproteinases (MMPs), precisely MMP-2, MMP-9, and MMP-14 have also been implicated to partake in the angiogenesis of new blood vessel during carcinogenesis (Figure 3). They are often associated with the indigenous secretion of VEGF\textsuperscript{52,60}. These MMPs embodies a sizeable group of cation-dependent metallo-endo- or metallo-exo-peptidases conscientious for synchronization of diverse biological activities associated with cancer pathogenesis\textsuperscript{52,61}. Studies have shown that multimerin 2 (MMRN2) blocks angiogenic propagation by repossessing VEGFA and discontinuing with the VEGF/VEGFR2 signaling axis\textsuperscript{62}. Further studies have proven that MMRN2 fits into the EMI domain endowed (EDEN) protein subgroup\textsuperscript{52,63}. Structurally, MMRN2 exhibits analogous molecular build-up; though, different from EDEN subgroups, its secretion is restricted in tight apposition with the EC superficially\textsuperscript{52,64}. Studies\textsuperscript{52} have indicated that MMRN2 fragmentation supports EC flexibility and emanating angiogenesis as well as foster elucidation on how this EC-specific molecule is synchronized during angiogenesis. We, therefore, propose further studies associating MMRN2 and HMGB1 in cancer since no data exist linking them. Schlueter et al\textsuperscript{55} demonstrated in their experiment with endothelial-sprouting assay that exogenous HMGB1 triggers endothelial cell migration and propagation \textit{in vitro} in a dose-dependent fashion. A study indicated that stimulation of HMGB1 and its receptor RAGE lead to the stimulation of NF-κB, which upregulates leukocyte adhesion molecules and the generation of proinflammatory cytokines and angiogenic factors in both hematopoietic and endothelial cells, thus facilitating inflammation and angiogenesis\textsuperscript{66}. Wake et al\textsuperscript{67} demonstrated that HMGB1 in multifaceted with heparin similarly triggers angiogenesis. Another study indicated that the consequence of HMGB1 is abolished when RAGE was down-regulation by antisense molecules\textsuperscript{68}. Further studies revealed that antibody focused HMGB1 blocked angiogenesis \textit{in vitro} and \textit{in vivo}\textsuperscript{69,70}.

\textbf{HMGB1 involvement in cancer metastasis and tissue invasion}

Studies have proven that HMGB1 and RAGE strappingly associated with metastasis and tissue invasion in many cancers (Figure 3). Moreover, RAGE is favorably secreted in inadequately differentiated cancer cells of numerous cancer tissues. Also, RAGE immunoreactivity is interrelated with complexity of invasion and lymph node metastasis in several cancers. Furthermore, during cancer development, RAGE-positive cancer cells are predominantly positioned at spots of active invasion as well as all lymphatic metastases\textsuperscript{39,44}. Additionally, studies have demonstrated that HMGB1/RAGE intercalations appear to be associated with the secretion of p44/p42, p38 and SAP/JNK MAP kinases beside MMPs, which are meticulously linked to kinase cascades (Figure 3)\textsuperscript{39,71}. Studies\textsuperscript{39,72,73} have further indicated that T lymphoma invasion and metastasis 1 (TIAM1) with a guanine nucleotide exchange factor activating RAC and other invasion-facilitating molecules such as Trophinin, trigger the amplification HMGB1 secretion too. Furthermore, the metastasis-facilitating factor E-selectin upregulates the secretion of HMGB1 to the extracellular milieu with a resultant amplification of E-selectin secretion\textsuperscript{39,74}. Also, the decreasing of immune defense system during carcinogenesis results in metastasis. Studies have proven that HMGB1 secretion during carcinogenesis results in diminished quantities of macrophages in lymph nodes and liver-specific antigen presenting Kupffer-cells\textsuperscript{39,75,76}. Furthermore, HMGB1/RAGE interrelation appears to lessen cancer cell migration \textit{in vitro} resulting in reduced metastasis in some cancer models (Figure 3)\textsuperscript{39,77}. The reasons for the above phenomenon could be due to diverse -COOH- binding terminals to RAGE or may be due to absence of precise modifying cancer environment in the human body\textsuperscript{39,77}. 

\textit{HMGB1 IN CARCINOGENESIS AND THERAPY}
that TLR-2, and not TLR-4 in DCs, intermediates the T-cell-dependent anti-cancer immune response that triggers glioma recession. Studies have proven that HMGB1 may bind to TIM-3 or encounter a redox modification with a resultant oxidized type, which may mediate immunogenic tolerance. Moreover, Luo et al.[] indicated that HMGB1 secretion during chemotherapy augments the capability of leftover tumor cells

Cancer cell death can be immunogenic or non-immunogenic based on the kind of anticancer therapy. Studies have proven that HMGB1 is secreted by dead or dying cells, which facilitate immunogenic cell death and consequent anti-cancer immunity and cancer clearance by binding to TLR4;[15,79]. Curtin et al.[] demonstrated that TLR-2, and not TLR-4 in DCs, intermediates the T-cell-dependent anti-cancer immune response that triggers glioma recession. Studies have proven that HMGB1 may bind to TIM-3 or encounter a redox modification with a resultant oxidized type, which may mediate immunogenic tolerance. Moreover, Luo et al.[] indicated that HMGB1 secretion during chemotherapy augments the capability of leftover tumor cells

**HMGB1 and cancer therapeutic potentials**

Cancer cell death can be immunogenic or non-immunogenic based on the kind of anticancer therapy. Studies have proven that HMGB1 is secreted by dead or dying cells, which facilitate immunogenic cell death and consequent anti-cancer immunity and cancer clearance by binding to TLR4. Curtin et al.[] demonstrated that TLR-2, and not TLR-4 in DCs, intermediates the T-cell-dependent anti-cancer immune response that triggers glioma recession. Studies have proven that HMGB1 may bind to TIM-3 or encounter a redox modification with a resultant oxidized type, which may mediate immunogenic tolerance. Moreover, Luo et al.[] indicated that HMGB1 secretion during chemotherapy augments the capability of leftover tumor cells

**Fig. 3.** HMGB1 and RAGE are secreted by cancer cells. HMGB1/RAGE intercalations are associated with the secretion of p44/p42, p38 and SAP/JNK MAP kinases beside MMPs, which are meticulously linked to kinase cascades leading to tissue invasion and metastasis in many cancers. T lymphoma invasion and metastasis 1 (TIAM1) with a guanine nucleotide exchange factor activating RAC, E-selectin and other invasion-facilitating molecules such as Tropinin, trigger the amplification of HMGB1 secretion. On the contrary, HMGB1/RAGE interrelation appears to lessen cancer cell migration in vitro resulting in reduced metastasis in some cancer models via diverse -COOH- binding terminals to RAGE. Matrix metalloproteinases (MMPs), precisely MMP-2, MMP-9, and MMP-14 have also been implicated to partake in the angiogenesis of new blood vessel during carcinogenesis. Therefore, HMGB1 and RAGE strappingly associated with metastasis and tissue invasion in many cancers.
to recur and metastasize in a RAGE-dependent fashion. Kang et al. further stress that blockage of the HMGB1-RAGE pathway increases the efficiency of chemotherapy. Cumulatively, numerous factors comprising of receptor, death type, and redox state define the action of HMGB1 in anti-tumor immune reaction. Several studies have established that focusing on HMGB1 ligand or its receptor epitomizes a key hypothetical function in cancer treatment, looking at its extensive secretion, as well as that of its receptor in practically all cancer categories reported in literature. Studies have proven that neutralizing anti-HMGBl antibodies block the secretion of TNF-α and IL-6 by inhibiting extracellular HMGB1 but do not block the release of HMGB1. This was evident in colitis-related cancer models where neutralizing antibodies to HMGB1 reduce cancer occurrence and magnitude. Advanced research revealed that inhibition of RAGE signaling pathways can also lead to reduction of cancer evolution and advancement and numerous modalities by which inhibition HMGB1-RAGE signaling occur have been demonstrated. This is evidenced in the delivering of extracellular ligand binding domain of sRAGE, inhibition of Fab fragments obtained from anti-RAGE and/or anti-HMGB1 IgG and production of transfected C6 glia secreting sRAGE.

Ethyl pyruvate blocks the secretion of TNF and HMGB1 from endotoxin-triggered RAW 264.7 murine macrophages, and decreases stimulation of p38 MAPK and NF-κB signaling pathways. Pre-treatment with ethyl pyruvate also inhibits endotoxin lethality and blocks the secretion of TNF and HMGB1. This has exhibited success in numerous disease disorders including lung adenocarcinoma cells. Platinum therapy typically generates dual modifications such as 1,2 intrastrand dGpG crosslink and a trifling 1,3 intrastrand dGpG modify. These two modifications are amendable by an expurgating reparation structure. The HMG domain motifs bind precisely to the key platinum DNA dGpG motif, generating a defense against the human expurgating nucleases consummated via the HMGB1 acidic domain. A key adverse effect of platinum therapy is ototoxicity, and HMGB1 has been exhibited to partake in cisplatin-stimulated ototoxicity in rats. Studies have shown that cancer cells nurtured with the platinating agent oxaliplatin maintained HMGB1 inside the nucleus for appreciably lengthier epochs than other agents used at similar cytotoxic strengths or even with effective cytolytic cells. Further studies have indicated that HMGB1 remain restrained at the nucleus at the early phases of cisplatin action during melanoma treatment, nevertheless, prolonged treatment of melanoma with cisplatin resulted in necrosis with appreciably elevated levels of HMGB1. Relatedly, in vitro findings in prime cultured rat hepatocytes revealed nontoxic quantities of cisplatin which confiscate HMGB1 within the nucleus of hypoxic cells and in vivo inhibited liver destruction.

Quercetin a 3,3',4',5,7-pentahydroxyflavone dehydrate derivative, which is an antioxidant, has anti-inflammatory properties, controls NO, IL-6 and TNF-α secretion, thus relieving oxidative injury in the tissue and blocking LPS triggers a deferment in extemporaneous apoptosis as well as stimulation of neutrophils. Studies have shown that quercetin action considerably decreases circulating levels of HMGB1 in animals with well-known endotoxemia. Furthermore, in macrophage cultures, quercetin blocked the secretion and cytokine actions of HMGB1 as well as restraining the stimulation of MAPK and NF-κB signaling pathways that are key for HMGB1-triggered consequent cytokine secretion. Moreover, quercetin and the autophagic blocker Wortmannin blocked LPS stimulated type II LC3 generation and accumulation in addition to HMGB1 translocation and secretion. Nevertheless, a variety of quercetin’s activities render it a hypothetical anti-cancer agent. These activities are; cell cycle regulation, interface at type II estrogen binding domains, and tyrosine kinase blockade. Several studies have proven that quercetin intermediates the down-regulation of mutant p53 and triggering of mitochondrial and caspase-3-dependent pathways in the human breast cancer cell line MDA-MB468.

Besides the principal responsibilities of extracellular HMGB1 in anticancer therapy, intracellular HMGB1 has overall negative regulatory efficiency of anticancer therapy. Studies have proven that HMGB1 is a unique curative focus in chemotherapy resistance. Downregulation of HMGB1 secretion by RNAi augmented the anticancer action of cytotoxic agents, while upregulation of HMGB1 secretion by gene transfection augmented drug resistance. Several studies have indicated that amplified HMGB1 secretion in cancer cells promotes chemotherapy resistance partially via blockade of apoptosis and facilitation of autophagy, which establish cell outcome in anticancer therapy. Nevertheless, HMGB1 vary in the rheostat of chemotherapy agent toxicity in cancer cells and normal cells. We propose further studies into these variations.
CONCLUSIONS

Intracellular and extracellular HMGB1 play meaningful roles in numerous cancers as outlined above. During the pathogenesis of cancer, HMGB1 has proven to be involved in several carcinogenic as well as anticancer activities. HMGB1 partakes in apoptosis, autophagy, growth as well as anti-growth signaling pathways, cancer immunity, angiogenesis, lymphangiogenesis, tissue invasion and metastasis during carcinogenesis. In line with the role of HMGB1 in the pathological process of numerous cancers above, we proposed HMGB1 could become a therapeutic target in cancer although further studies are required to arrive at conclusions.

CONFLICT OF INTEREST:
All the authors declare no conflict of interest.

AUTHORS’ CONTRIBUTIONS:
S.A.R is guarantors of integrity of the entire manuscript. ZS, and HX contributed equally to this manuscript. LHX, JXY, ZS, YJ, JW contributed concepts and design. SAR wrote the final manuscript. ZS, and HX contributed equally to the intellectual content of the manuscript.

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